Cancer Causes and Control **10**: 143–155, 1999.

A pooled analysis of case-control studies of thyroid cancer

II. Menstrual and reproductive factors

Eva Negri[1,*], Luigino Dal Maso[2], Elaine Ron[3,*], Carlo La Vecchia[1,4], Steven D. Mark[3], Susan Preston-Martin[5], Anne McTiernan[6], Laurence Kolonel[7], Yasuhiko Yoshimoto[8], Fan Jin[9], Gun Wingren[10], Maria Rosaria Galanti[11], Lennart Hardell[12], Eystein Glattre[13], Eiliv Lund[14], Fabio Levi[15], Dimitrios Linos[16], Claudia Braga[1] & Silvia Franceschi[2]

[1]*Laboratory of General Epidemiology, Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea, 62, 20157 Milan, Italy (E-mail: EVANEGRI@IRFMN.MNEGRI.IT);* [2]*Centro di Riferimento Oncologico, 33081 Aviano, PN, Italy;* [3]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Executive Plaza South, 6120 Executive Boulevard, Rockville, MD 20852, USA (E-mail: RONE@EPNDCE.NCI.NIH.GOV);* [4]*Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, 20133 Milan, Italy;* [5]*Department of Preventive Medicine, University of Southern California, Los Angeles, CA 90033-0800, USA;* [6]*Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024, USA;* [7]*University of Hawaii at Manoa, Cancer Research Center of Hawaii, Honolulu, Hawaii 96813, USA;* [8]*National Institute of Radiological Sciences, 263-0024 Chiba, Japan;* [9]*Shanghai Cancer Institute, Shanghai, People's Republic of China;* [10]*Division of Occupational and Environmental Medicine, Faculty of Health Sciences, Linköping University, SE-581 85 Linköping, Sweden;* [11]*Department of Cancer Epidemiology, University Hospital, SE-57185 Uppsala, Sweden (Current address: Tobacco Prevention Centre, SE-141 57 Huddinge Sweden);* [12]*Department of Oncology, Örebro Medical Center, SE-701 85 Örebro, Sweden;* [13]*The Cancer Registry of Norway, Montebello, NO-3010 Oslo, Norway;* [14]*Institute of Community Medicine, University of Tromsø, NO-9037 Tromsø, Norway;* [15]*Registre Vaudois des Tumeurs, CH-1011 Lausanne, Switzerland;* [16]*Institute of Preventive Medicine, GR-145 61 Kifissia, Greece (*Authors for correspondence)*

Received 20 July 1998; accepted in revised form 9 November 1998

Key words: case-control studies, menarche, menopause, pregnancy, thyroid cancer.

Abstract

Objective: It has been suggested that female hormones, and hence menstrual and reproductive factors, play a role in thyroid cancer etiology. Epidemiological data, however, are limited and inconsistent, partly because of the small number of cases included in each study. To clarify the etiology of thyroid cancer, we conducted a pooled analysis of original data from 14 case-control studies, 4 from the United States, 2 from Asia, and 8 from Europe.
Methods: This analysis included a total of 2,247 female cases of thyroid cancer (80% papillary) and 3,699 control women. Pooled odds ratios (OR) were estimated using logistic regression, conditioning on study and (i) matching sets for individually matched studies, or (ii) quinquennia of age for the other studies. Additional terms for age and history of radiation exposure were included in the regression equations.
Results: The OR per year of later menarche was 1.04 (95% confidence interval (CI) 1.0–1.1). Compared to pre-menopausal women, the OR was 1.3 for women with natural menopause, and 1.8 for those with artificial menopause, but the studies were heterogeneous and the association may be due, at least in part, to diagnostic or ascertainment bias. Parity, spontaneous or induced abortions and history of infertility were not associated with thyroid cancer risk. The OR was above unity in women reporting later age at first birth (OR = 1.1, 95% CI 1.0–1.3 for 5-year delay) and higher in the first years after a birth.
Conclusions: The associations of menstrual and reproductive factors with thyroid cancer risk were generally weak, but appeared stronger among women diagnosed with thyroid cancer at younger ages.

Introduction

Thyroid cancer is approximately three times more frequent in women than in men, particularly during reproductive years [1, 2]. Elevated thyroid stimulating hormone (TSH) secretion has been reported during puberty, pregnancy and oral contraceptive use [3–6], and elevated levels of TSH are associated with thyroid growth in humans [7, 8]. Moreover, during puberty and the menstrual cycle, changes occur in the thyroid gland [9]. Estrogen receptors have been found in thyroid cancers, particularly in well differentiated ones [10–12]. Estrogens can promote thyroid tumors in animals [13]. These findings have led to the hypothesis that sex hormones, and consequently menstrual and reproductive events, modify a woman's risk of thyroid cancer.

Results from epidemiological studies, however, have been inconsistent. Some investigators found an increasing risk of thyroid cancer with increasing number of pregnancies or births [14–18], while others did not [19–23]. A record linkage study on 1.1 million Norwegian women born 1935–1969 found a direct relation with parity [24] and a Swedish nested case-control study of over 1,400 cases reported an association between parity and thyroid cancer risk for women aged 50 to 59 years at diagnosis, but not at younger ages [25]. Late menarche [21], post-menopausal status and artificial menopause [14–16, 26], late age at first or last birth [20, 21, 25], personal history of miscarriages [14–16, 20, 22] or history of miscarriages in the mother [27], and difficulties in conception [22] have also been suggested as risk factors for thyroid cancer, but the evidence is scanty and inconsistent.

To investigate further the relation between menstrual and reproductive factors and thyroid cancer risk, we conducted a pooled analysis of 14 thyroid cancer case-control studies.

Methods

A detailed description of the studies included in this pooled analysis is given in a separate paper [28] and in the original study publications. The 14 studies included represent all case-control studies on thyroid cancer identified through MEDLINE searches and published between 1980 and 1997, or personal knowledge of authors. Four studies were conducted in the USA, including one in Los Angeles [14], one in Western Washington [19], one in Hawaii [22], and one in Connecticut [20]. Two were conducted in Asia, one in Hiroshima and Nagasaki, Japan, and the other in Shanghai, China [16]. In the Japanese study, cases and controls were matched on A-bomb exposure and radi-

Table 1. Selected descriptive characteristics of menstrual factors by study (cases:controls)

Study number and location	No. of cases and controls	Median age at menarche	% of postmenopausal women	Median age at menopause	% with artificial menopause[a]
America – USA					
1. Los Angeles	292:292	13:12	16:14	42:40	81:60
2. Western Washington	185:393	13:13	46:37	43:47	59:48
3. Hawaii	140:328	13:13	45:41	45:48	41:40
4. Connecticut	109:208	13:13	43:40	46:47	37:45
Asia					
5. Hiroshima and Nagasaki, Japan	307:307	14:14	32:31	48:49	25:19
6. Shanghai, China	207:207	15:15	14:9	48:47	13:5
Europe – North					
7. Southeastern Sweden	149:187	13:14	–	–	–
8. Uppsala, Sweden	133:203	13:13	35:34	51:50	27:16
9. Northern Sweden	123:240	13:13	–	–	–
10. Norway, NHSS	71:355	–	–	–	–
11. Tromsø, Norway	58:138	14:13	31:31	47:50	35:10
Europe – South					
12. Northern Italy	291:427	13:13	40:43	49:49	29:23
13. Vaud, Switzerland	100:318	13:13	39:43	47:50	49:22
14. Athens, Greece	82:96	13:13	34:22	49:50	29:38
Total	2247:3699	13:13	32:33	47:48	39:31

[a] Among postmenopausal women.
– Means data not available.

Table 2. Selected descriptive characteristics of reproductive factors by study (cases:controls)

Study number and location	No. of cases and controls	% of parous women	Mean no. of births	Mean no of abortions	% with history of infertility	Median age at first birth[a]	Median age at last birth[a]	Median years since last birth[a,b]	% who ever breastfed[a]
America – USA									
1. Los Angeles	292:292	61:59	1.4:1.5	0.6:0.5	2:3	23:22	27:27	6:8	43:49
2. Western Washington	185:393	77:74	2.1:1.9	0.5:0.5	15:18	22:22	28:27	5:5	82:82
3. Hawaii	140:328	74:77	2.4:2.1	0.4:0.3	17:14	24:24	30:29	9:6	74:71
4. Connecticut	109:208	80:68	2.0:1.9	0.5:0.4	21:19	23:23	28:29	7:8	40:44
Asia									
5. Hiroshima and Nagasaki, Japan	307:307	80:80	2.0:1.8	1.0:0.9	5:3	24:24	29:29	13:13	94:91
6. Shanghai, China	207:207	70:63	1.3:1.3	0.3:0.2	–	25:25	–	–	–
Europe – North									
7. Southeastern Sweden	149:187	–	–	–	–	23:24[c]	–	–	–
8. Uppsala, Sweden	133:203	77:75	1.7:1.6	0.4:0.4	–	23:23	28:28	7:10	–
9. Northern Sweden	123:240	–	–	–	–	22:22[c]	–	–	–
10. Norway, NHSS	71:355	95:90	2.8:2.8	–	–	23:23	–	–	–
11. Tromsø, Norway	58:138	84:87	2.5:2.3	0.4:0.5	–	22:21	27:29	7:7	96:96
Europe – South									
12. Northern Italy	291:247	75:72	1.7:1.7	0.4:0.5	1:0	25:24	30:29	8:9	–
13. Vaud, Switzerland	100:318	68:68	1.5:1.5	0.6:0.4	4:3	24:24	28:28	11:9	–
14. Athens, Greece	82:96	74:56	1.6:1.1	1.5:1.1	–	24:23	–	–	89:83
Total	2247:3699	74:73	1.8:1.8	0.6:0.5	8:8	24:23	29:28	8:8	77:76

[a] Nulliparae excluded.
[b] Women aged 45 years or less.
[c] Mean age at first pregnancy.
– Means data not available.

Table 3. Distribution[a] of thyroid cancers and controls and corresponding odds ratios (OR)[b] according to menstrual factors

Variable	Cases	Controls	OR (95% CI)[c]
Age at menarche (years)			
< 13	663 (31)[d]	1153 (35)	1[e]
13–14	941 (44)	1425 (43)	1.1 (1.0–1.3)
≥ 15	542 (25)	726 (22)	1.2 (1.0–1.4)
χ^2 heterogeneity across studies 8.10; 12df ($p = 0.78$)			
per year increase			1.0 (1.0–1.1)
χ^2 heterogeneity across studies 10.25; 12df ($p = 0.59$)			
Menopausal status[f]			
Pre	1282 (68)	1943 (67)	1[e]
Post, natural	372 (20)	666 (23)	1.3 (1.0–1.8)
Post, artificial	236 (12)	296 (10)	1.8 (1.4–2.4)
χ^2 heterogeneity across studies 27.28; 20df ($p = 0.13$)			
Age at menopause (years)[g]			
< 45	209 (35)	260 (28)	1[e]
45–49	170 (29)	260 (28)	0.9 (0.7–1.3)
50–52	136 (23)	242 (26)	0.8 (0.6–1.2)
≥ 53	77 (13)	172 (18)	0.8 (0.5–1.2)
χ^2 heterogeneity across studies 22.98; 10df ($p = 0.01$)			
per 5 years increase			1.0 (0.9–1.1)
χ^2 heterogeneity across studies 20.91; 10df ($p = 0.02$)			
Time since menopause (years)[g]			
≤ 3	121 (21)	145 (16)	1.5 (1.0–2.2)
4–6	86 (15)	123 (13)	1.1 (0.8–1.7)
7–9	67 (11)	121 (13)	0.9 (0.6–1.3)
≥ 10	316 (54)	545 (58)	1[e]
χ^2 heterogeneity across studies 11.79; 10df ($p = 0.30$)			
per 5 years increase			1.0 (0.9–1.1)
χ^2 heterogeneity across studies 21.34; 10df ($p = 0.02$)			

[a] Based on studies 1–9, 11–14 for age at menarche; 1–6, 8, 11–14 for menopausal status, age at menopause and time since menopause.
[b] Estimates from conditional logistic regression conditioned on study and age, and adjusted for history of radiation and age.
[c] 95% confidence interval.
[d] The percentage is given in parentheses.
[e] Reference category.
[f] Adjusted also for use of hormone replacement therapy.
[g] Adjusted also for type of menopause.

ation dose. Of the eight European studies, five were conducted in Scandinavian countries, three in Sweden [17, 23, 26, 29] and two in Norway [26, 29, 30], and the remaining three in Northern Italy [21], the Swiss canton of Vaud [15], and Athens, Greece [31].

In this paper, only women were considered, for a total of 2,247 cases and 3,699 controls. A large majority of the cases were papillary (1,791; 79.7%) followed by follicular (315; 14.0%), medullary (39; 1.7%), and anaplastic (11; 0.5%). Other histologic types (22) comprised 1.0% of the cases and histology was undefined for 69 (3.1%).

The original datasets were restructured to conform to a predefined uniform format, and analyzed in a standardized way. The variables considered were age at menarche, menopausal status, age at menopause, type of menopause (natural/other), history of and age at hysterectomy, monolateral or bilateral oophorectomy, number of pregnancies, births, miscarriages and induced abortions, outcome of first pregnancy, age at first and last pregnancy and birth, number of children breast fed, duration of breast feeding and history of infertility.

For each variable, a set of tables was produced for each study. These included: (i) descriptive features of the distribution for cases and controls separately, including mean, standard deviation, quantiles, range; (ii) the frequency distribution of cases and controls according to predefined categories; (iii) the odds ratios (OR) and the corresponding 95% confidence intervals (CI), estimated using conditional logistic regression models [32]. For matched studies, the strata were defined by the matching sets, and for unmatched ones, by quinquennia of age. Data for the 14 studies were analyzed together, with conditional logistic regression models, conditioning on study. Heterogeneity among studies, geographical areas and study design was systematically tested by comparing the difference in the −2 log likelihood of a

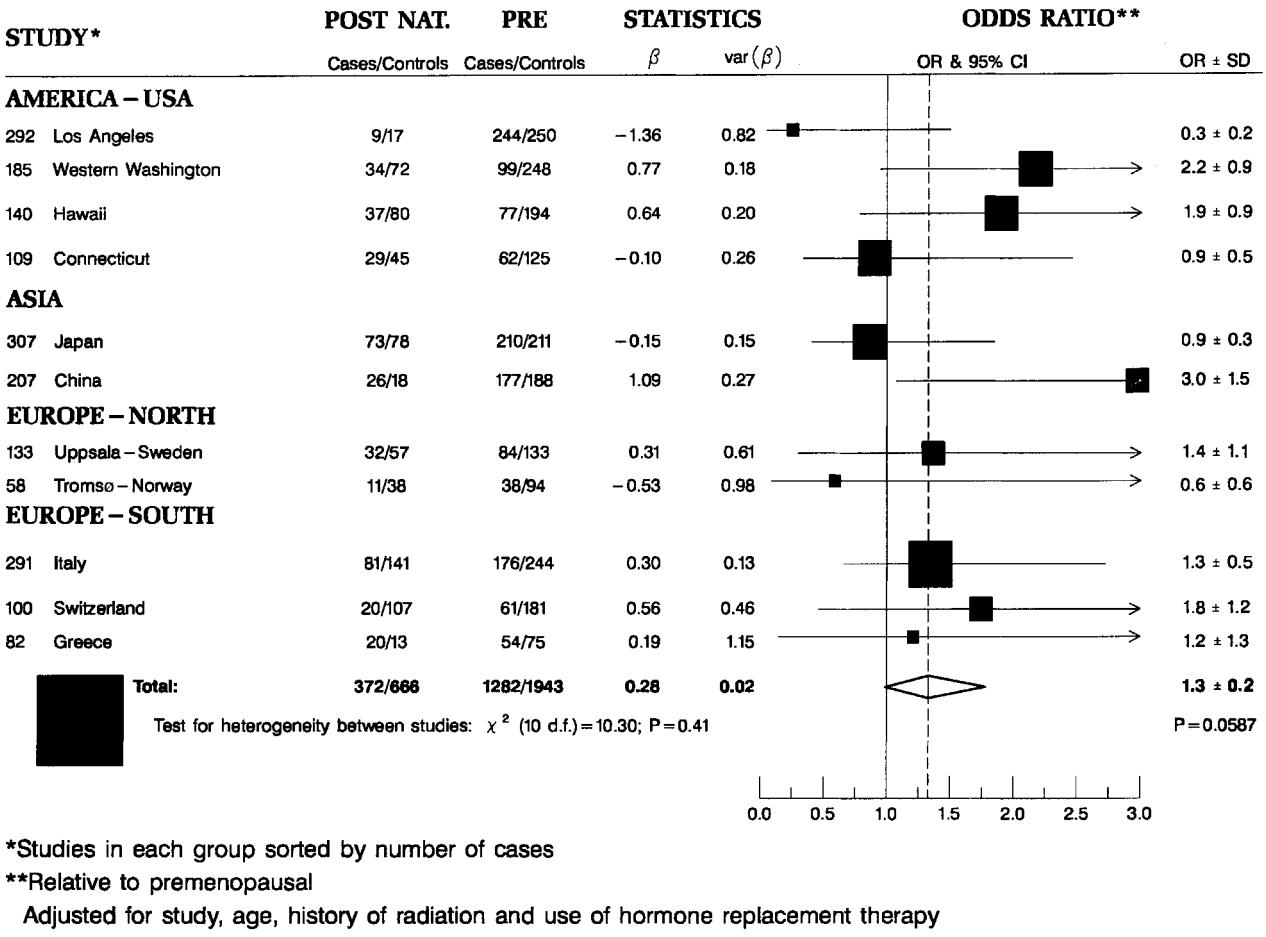

Fig. 1. Odds ratio of thyroid cancer in women reporting natural menopause as compared to pre-menopausal ones.

model estimating a common OR and a model estimating an OR for each group to the chi-square distribution with degrees of freedom equal to the number of groups minus one. For categorical variables with ordinal values, the heterogeneity among trends was tested.

Since all American and Scandinavian studies had population controls, while the three South European ones used hospital controls, the heterogeneity test between geographical areas and study designs were similar, and only the former were presented. The modifying effect of age at diagnosis was tested by computing the decrease in −2 log likelihood between the models without and with interaction terms, assuming that this follows a chi-square distribution with degrees of freedom given by the number of interaction terms. Papillary and follicular cancers also were analyzed separately.

For some binary or continuous variables, graphs are presented displaying the odds ratio for each study, plotted as a black square whose size is inversely proportional to the variance of the estimate [33].

Results

Selected descriptive data on menstrual factors in various studies considered are given in Table 1. Age at menarche occurred somewhat later in Asia than in other continents. Although the menopause-related variables reflected the different age distribution of subjects in various studies, cases reported a slightly earlier age at menopause and higher percentage of artificial menopause than controls in several studies. Mean parity was somewhat lower in southern Europe than other geographic areas (Table 2). The proportion of women reporting a history of infertility was highest in Hawaii, Washington State and Connecticut, probably reflecting differences in the diagnosis of the condition, or in the type of information collected.

The distribution of thyroid cancer cases and controls according to menstrual factors, and the corresponding ORs, are presented in Table 3. There was a moderate association between later age at menarche and thyroid cancer risk: the OR was 1.2 for women whose

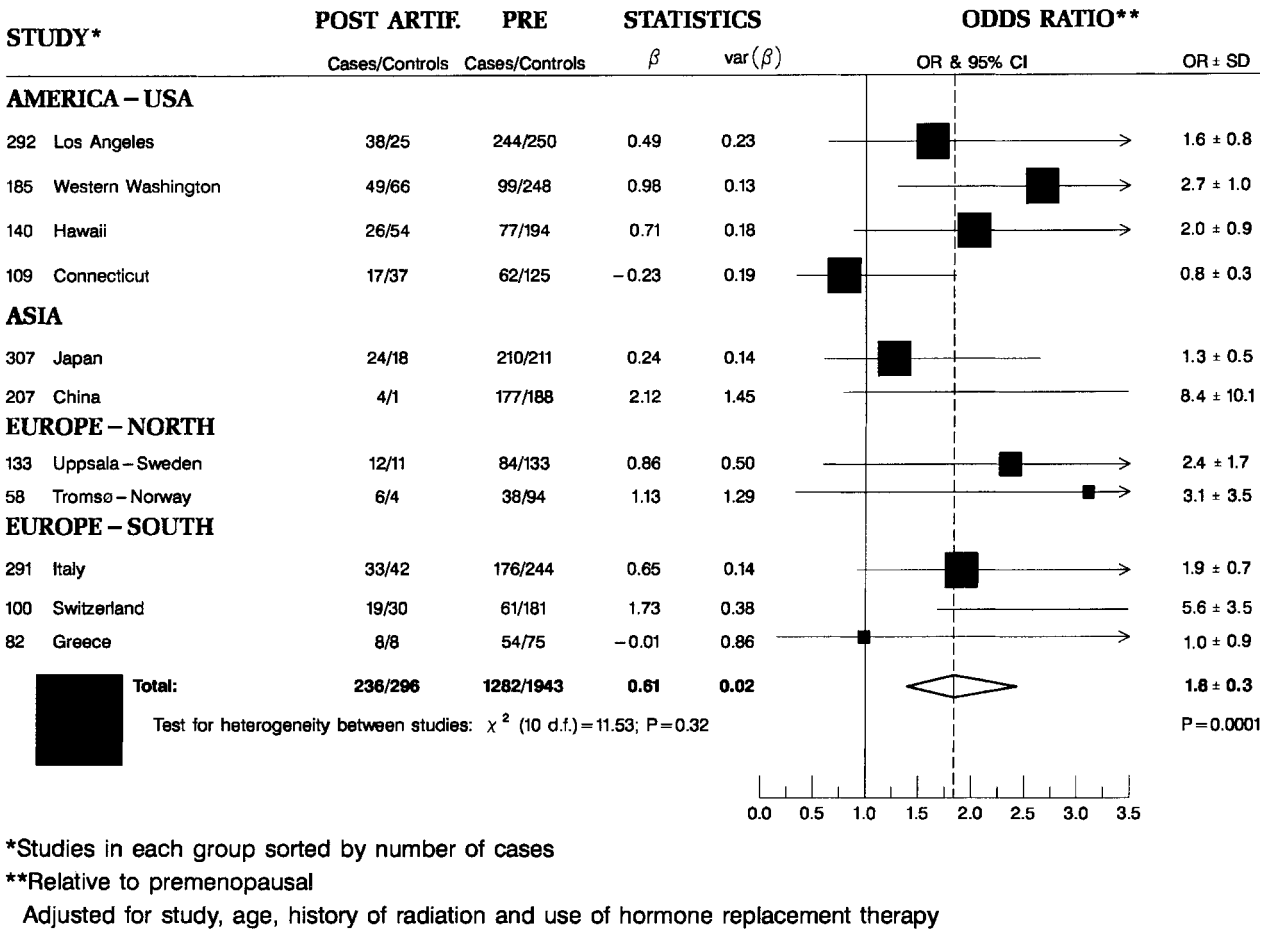

Fig. 2. Odds ratio of thyroid cancer in women reporting artificial menopause as compared to pre-menopausal ones.

menarche occurred at age 15 or more years compared with those reporting menarche below age 13. The OR per year of later menarche was 1.0 (95% CI 1.0 to 1.1).

Compared with pre-menopausal women, the OR was above one for both natural and artificial menopause (Figures 1 and 2), and the association was statistically significant for artificial menopause (OR = 1.8, 95% CI 1.4 to 2.4, Figure 2). The association with menopausal status, however, was restricted to women who had not received radiation exposure.

Thyroid cancer risk was somewhat lower in women with later menopause, the OR being 0.8 for women reporting menopause at age 50 or over. The OR for a 5-year delay in age at menopause was 1.0 (not significant); however, significant heterogeneity among studies was observed. Although the estimate was not significant, the OR was above unity for women reporting menopause ≤ 3 years before diagnosis, and the OR tended to decline with increasing time since menopause.

Parous women compared with nulliparous women had an increased risk of borderline significance; the pooled OR was 1.2 ($p = 0.08$) (Table 4, Figure 3). No clear relationship with number of births was seen. The ORs were 1.3, 1.2, 1.1, and 1.2 for women with 1, 2, 3 and 4 or more births, respectively, compared with nulliparae. Similarly, there was no appreciable relationship with miscarriages (OR = 1.0 for ≥ 2 miscarriages), induced abortions (OR = 1.1 for ≥ 2 abortions), or history of infertility (OR = 1.2).

Compared to nulligravidae, the OR was 1.3, 1.3 and 1.8 respectively for women whose first pregnancy ended up with a birth, an induced abortion or a miscarriage.

The risk of thyroid cancer increased with increasing age at first birth: compared to women whose first birth was below age 20, the OR was 0.9 for women whose first birth was at age 20 to 24, 1.1 at 25 to 29, and 1.3 at ≥ 30 years. In 10 out of 12 studies, the OR was above unity in women with late age at first birth, and the continuous OR for a 5-year increase was 1.1 (95% CI 1.0 to 1.3,

Table 4. Distribution[a] of thyroid cancers and controls and corresponding odds ratios (OR)[b] according to reproductive factors

Variable	Cases	Controls	OR (95% CI)[c]
Number of births[d]			
Nulliparae	503 (26)[e]	861 (27)	1[f]
Parae	1451 (74)	2379 (73)	1.2 (1.0–1.4)
χ^2 heterogeneity across studies 10.18; 11df ($p = 0.51$)			
1	357 (18)	507 (16)	1.3 (1.0–1.6)
2	558 (29)	903 (28)	1.2 (1.0–1.4)
3	282 (14)	513 (16)	1.1 (0.9–1.4)
≥ 4	250 (13)	445 (14)	1.2 (1.0–1.6)
χ^2 heterogeneity across studies 6.50; 11df ($p = 0.83$)			
per birth			1.0 (1.0–1.1)
χ^2 heterogeneity across studies 5.37; 11df ($p = 0.91$)			
Number of miscarriages[g]			
0	1356 (79)	2081 (81)	1[f]
1	256 (15)	329 (13)	1.2 (1.0–1.5)
≥ 2	96 (6)	158 (6)	1.0 (0.8–1.3)
χ^2 heterogeneity across studies 4.99; 8df ($p = 0.76$)			
per miscarriage			1.0 (0.9–1.1)
χ^2 heterogeneity across studies 6.11; 8df ($p = 0.64$)			
Number of induced abortions[g]			
0	1379 (81)	2181 (85)	1[f]
1	199 (12)	241 (9)	1.1 (0.9–1.4)
≥ 2	130 (8)	145 (6)	1.1 (0.8–1.4)
χ^2 heterogeneity across studies 12.25; 8df ($p = 0.14$)			
per induced abortion			1.1 (1.0–1.2)
χ^2 heterogeneity across studies 11.66; 8df ($p = 0.17$)			
Outcome of first pregnancy[g]			
Nulligravidae	261 (23)	424 (26)	1
Birth	687 (62)	1002 (62)	1.3 (1.0–1.8)
Induced abortion	80 (7)	103 (6)	1.3 (0.9–2.0)
Miscarriage	9 (8)	93 (6)	1.8 (1.2–2.6)
χ^2 heterogeneity across studies 22.14; 14df ($p = 0.08$)			
History of infertility[g]			
No	1142 (92)	1903 (92)	1[f]
Yes	98 (8)	173 (8)	1.2 (0.9–1.6)
χ^2 heterogeneity across studies 4.53; 6df ($p = 0.61$)			
Age at first birth[g]			
Nulliparae	503 (27)	861 (28)	0.9 (0.7–1.2)
< 20	156 (8)	273 (9)	1[f]
20–24	581 (32)	1083 (35)	0.9 (0.7–1.1)
25–29	434 (24)	673 (22)	1.1 (0.8–1.4)
≥ 30	161 (9)	214 (7)	1.3 (1.0–1.8)
χ^2 heterogeneity across studies 12.25; 11df ($p = 0.35$)			
per 5 years increase			1.1 (1.0–1.3)
χ^2 heterogeneity across studies 14.32; 11df ($p = 0.22$)			
Age at last birth[g]			
Nulliparae	416 (28)	708 (28)	1.0 (0.8–1.3)
< 25	205 (14)	383 (15)	1[f]
25–29	402 (27)	671 (27)	1.1 (0.9–1.4)
30–34	295 (20)	459 (18)	1.1 (0.9–1.4)
≥ 35	175 (12)	281 (11)	1.1 (0.9–1.6)
χ^2 heterogeneity across studies 10.47; 8df ($p = 0.23$)			
per 5 years increase			1.1 (1.0–1.2)
χ^2 heterogeneity across studies 8.38; 8df ($p = 0.40$)			
Years since last birth[g] (women aged ≤ 45 years)			
Nulliparae	332 (39)	556 (40)	1[f]
< 5	161 (19)	262 (19)	1.0 (0.7–1.4)
5–9	129 (15)	210 (15)	0.8 (0.6–1.3)

Table 4. (Continued)

Variable	Cases	Controls	OR (95% CI)[c]
10–14	118 (14)	182 (13)	0.9 (0.6–1.3)
≥ 15	103 (12)	164 (12)	0.8 (0.5–1.2)
χ^2 heterogeneity across studies 5.43; 8df (p = 0.71)			
per 5 years increase			0.9 (0.8–1.0)
χ^2 heterogeneity across studies 13.00; 8df (p = 0.11)			
Breast feeding[h] (parous women only)			
Never	178 (23)	287 (24)	1[f]
Ever	589 (77)	907 (76)	1.0 (0.7–1.3)
χ^2 heterogeneity across studies 4.59; 6df (p = 0.60)			
per 12 months increase			1.1 (1.0–1.2)
χ^2 heterogeneity across studies 11.05; 6df (p = 0.09)			

[a] Based on studies 1–6, 8, 10–14 for parity and age at first birth; 1–6, 12–14 for number of miscarriages and induced abortions: 1–6 for outcome of first pregnancy; 1–5, 8, 11–13 for age at and years since last birth; 1–5, 12, 13 for history of infertility; 1–5, 11, 14 for breast feeding.
[b] Estimates from conditional logistic regression conditioned on study and age, and adjusted for history of radiation and age.
[c] 95% confidence interval.
[d] Adjusted also for oral contraceptive use.
[e] The percentage is given in parentheses.
[f] Reference category.
[g] Adjusted also for parity.
[h] Adjusted also for parity and use of hormones for lactation suppression.

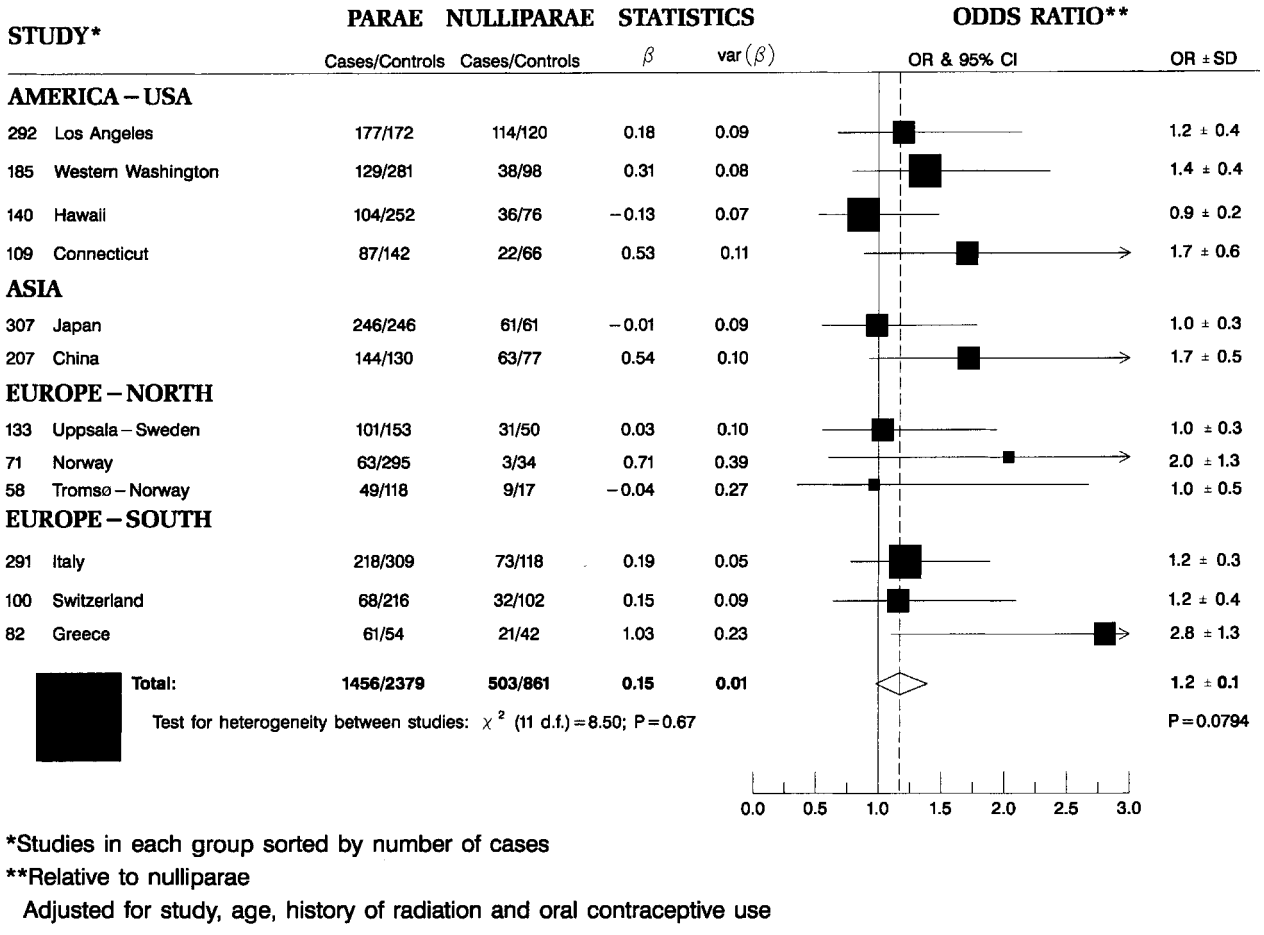

Fig. 3. Odds ratio of thyroid cancer in parous women as compared to nulliparae.

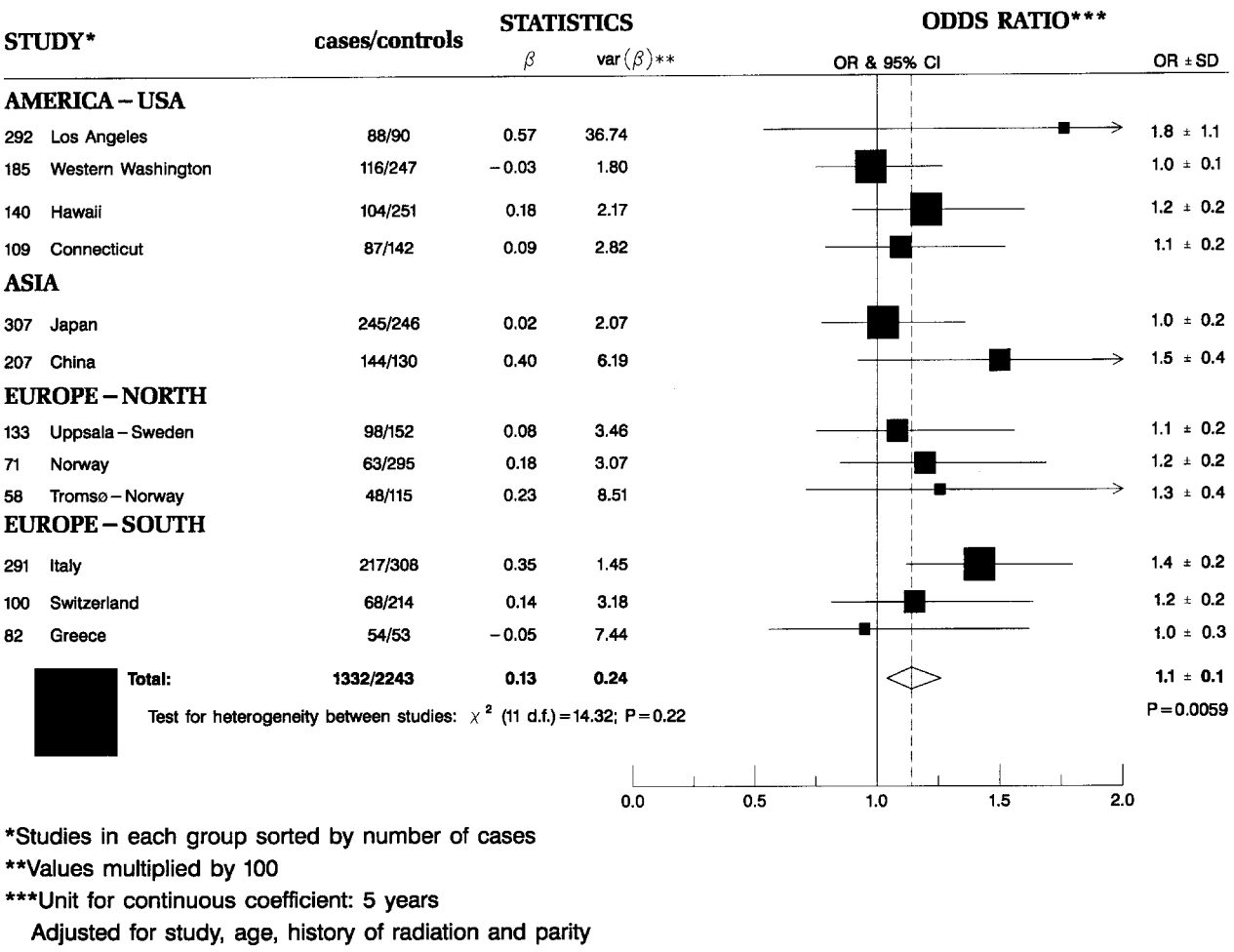

Fig. 4. Odds ratio of thyroid cancer for a 5-year delay of age at first birth.

Figure 4), but there was only a moderate association for a longer interval between menarche and first birth (OR = 1.1 (n.s.) for ≥ 11 years versus <8). There was also a tendency for thyroid cancer risk to increase with increasing age at last birth, although the trend was not significant. In women below age 45, the risk of thyroid cancer somewhat decreased with longer time since last birth, and the OR was 0.9 (95% CI 0.8 to 1.0) for a 5-year increase in time since last birth. There was no association between history of breast feeding and thyroid cancer risk; the OR for ever versus never breast feeding was 1.0. No significant interaction between reproductive factors and history of medical radiation therapy was observed.

The role of menopausal status, age at menopause, time since menopause, outcome of first pregnancy, age at first and time since last birth were further considered for papillary and follicular neoplasms separately (Table 5). Most associations were somewhat stronger for follicular neoplasms, but the patterns were similar, and the difference seen between the two most common histologic types were within the range of random variation.

Separate analyses in strata of geographical area and age at diagnosis showed no appreciable heterogeneity by geographic area (Table 6). Age at diagnosis, however, showed a significant interaction with menopausal status, time since menopause and age at last birth. In general, the associations with reproductive variables were systematically stronger at younger age, and declined with advancing age at thyroid cancer diagnosis. Thus, the OR for parae versus nulliparae was 1.3 at age 35 or under but 1.1 above 55, that for induced abortion 1.2 at age 35 or under and 1.0 above age 55, that for 5-year delay of age at first birth 1.3 at age 35 or under and 1.0 above age 55, and that for a 5-year increase in age at last birth 1.4 at age 35 or under, and 1.0 above age 55.

Table 5. Distribution[a] of papillary and follicular thyroid cancers and controls and corresponding odds ratios (OR)[b] according to menstrual and reproductive factors

Variable	Papillary			Follicular		
	Cases	Control	OR(95% CI)[c]	Cases	Controls	OR(95% CI)[c]
Menopausal status[e]						
Pre	1069	1813	1[d]	160	928	1[d]
Post, natural	280	629	1.2 (0.9–1.7)	58	441	1.6 (0.8–3.0)
Post, artificial	177	288	1.7 (1.3–2.3)	49	218	3.1 (1.7–5.6)
χ^2 heterogeneity across studies 26.91; 20df ($p = 0.14$)						
Age at menopause[f]						
< 45	152	247	1[d]	48	188	1[d]
45–49	126	247	0.9 (0.6–1.2)	31	175	1.0 (0.5–1.9)
50–52	110	230	0.9 (0.6–1.3)	15	170	0.5 (0.2–1.0)
≥ 53	55	165	0.8 (0.5–1.3)	13	109	0.8 (0.3–1.8)
χ^2 heterogeneity across studies 31.90; 10df ($p < 0.001$)						
per 5 years			1.0 (0.9–1.1)			0.9 (0.8–1.1)
χ^2 heterogeneity across studies 25.59; 10df ($p = 0.004$)						
Time since menopause[f]						
≤ 3	97	143	1.5 (1.0–2.4)	19	99	1.3 (0.6–2.9)
4–6	69	118	1.3 (0.8–2.0)	12	74	0.9 (0.4–2.2)
7–9	49	118	0.9 (0.6–1.4)	14	85	0.9 (0.4–1.9)
≥ 10	226	510	1[d]	62	384	1[d]
χ^2 heterogeneity across studies 16.44; 10df ($p = 0.09$)						
per 5 years			1.0 (0.9–1.1)			1.1 (0.9–1.3)
χ^2 heterogeneity across studies 23.88; 10df ($p = 0.008$)						
Outcome of first pregnancy[g]						
Nulligravidae	215	383	1[d]	38	176	1[d]
Birth	581	957	1.4 (1.0–1.9)	87	562	0.9 (0.4–1.8)
Induced abortion	68	100	1.2 (0.8–1.9)	8	47	1.0 (0.4–2.7)
Miscarriage	73	91	1.7 (1.1–2.7)	12	45	1.7 (0.7–4.3)
χ^2 heterogeneity across studies 22.01; 14df ($p = 0.08$)						
Age at first birth[g]						
Nulliparae	408	792	0.9 (0.7–1.3)	69	411	1.2 (0.6–2.6)
< 20	122	251	1[d]	26	155	1[d]
20–24	481	984	0.9 (0.7–1.2)	64	524	0.7 (0.4–1.3)
25–29	358	612	1.1 (0.9–1.5)	53	319	1.0 (0.6–1.9)
≥ 30	112	194	1.2 (0.8–1.7)	28	119	1.7 (0.9–3.5)
χ^2 heterogeneity across studies 14.44; 11df ($p = 0.21$)						
per 5 years			1.1 (1.0–1.3)			1.2 (1.0–1.5)
χ^2 heterogeneity across studies 18.50; 11df ($p = 0.007$)						
Years since last birth[g] (women aged ≤ 45 years)						
Nulliparae	275	521	1[d]	46	282	1[d]
< 5	134	255	1.0 (0.7–1.5)	23	175	0.6 (0.3–1.4)
5–9	106	206	0.9 (0.5–1.3)	19	116	0.8 (0.3–2.2)
10–14	99	161	0.9 (0.6–1.4)	13	100	0.5 (0.2–1.3)
≥ 15	85	157	0.8 (0.5–1.3)	11	89	0.4 (0.1–1.1)
χ^2 heterogeneity across studies 6.59; 8df ($p = 0.58$)						
per 5 years			0.9 (0.8–1.1)			0.9 (0.7–1.2)
χ^2 heterogeneity across studies 11.89; 8df ($p = 0.16$)						

[a] Based on studies 1–6, 8, 11–14 for menopausal status, age at menopause and time since menopause; 1–6 for outcome of first pregnancy; 1–6, 8, 10–14 for age at first birth; 1–5, 8, 11–13 for years since last birth; 1–5, 12, 13 for history of infertility.

[b] Estimates from conditional logistic regression conditioned on study and age, and adjusted for history of radiation and age.

[c] 95% confidence interval.

[d] Reference category.

[e] Adjusted also for use of hormone replacement therapy.

[f] Adjusted also for type of menopause.

[g] Adjusted also for parity.

Table 6. Odds ratio (OR)[a] of thyroid cancer according to selected menstrual and reproductive factors, in strata of geographical area and age at diagnosis

Variable	Geographical area				Age at diagnosis		
	USA	ASIA	North EU	South EU	≤ 35	36–55	≥ 56
Age at menarche							
per year	1.1	1.1	1.0	1.1	1.1	1.0	1.1
χ^2	0.9[b]; 3df ($p = 0.82$)				4.6[c]; 2df ($p = 0.10$)		
Menopausal status[d]							
pre	1[e]	1[e]	1[e]	1[e]	1[e]	1[e]	1[e]
post, natural	1.3	1.4	1.0	1.4	0.2	1.5	0.6
post, artificial	1.6	1.8	2.5	2.3	1.4	2.2	0.9
χ^2	3.5[b]; 6df ($p = 0.75$)				11.7[c]; 4df ($p = 0.02$)		
Age at menopause[f]							
per 5 years	0.9	1.0	1.3	1.0	–	1.0	0.9
χ^2	2.5[b]; 3df ($p = 0.47$)				0.3[c]; 1df ($p = 0.59$)		
Time since menopause[f]							
≤ 3	1.0	3.1	1.8	1.6	–	1.3	1.7
4–6	0.7	2.4	0.7	1.8	–	1.3	0.9
7–9	0.5	1.5	2.4	0.9	–	0.7	1.0
≥ 10	1[e]	1[e]	1[e]	1[e]	–	1[e]	1[e]
χ^2	1.5[b]; 3df ($p = 0.71$)				4.9[c]; 1df ($p = 0.03$)		
Parity[g]							
Nulliparae	1[e]	1[e]	1[e]	1[e]	1[e]	1[e]	1[e]
Parae	1.1	1.3	1.1	1.3	1.3	1.1	1.1
χ^2		1.6; 3df ($p = 0.66$)			1.6[c]; 2df ($p = 0.46$)		
per birth	1.0	1.0	1.0	1.1	1.1	1.1	1.0
χ^2	0.5[b]; 3df ($p = 0.92$)				4.6[c]; 2df ($p = 0.10$)		
Number of miscarriages[h]							
per miscarriage	1.1	1.0	–	1.0	1.1	1.0	1.0
χ^2	0.9[b]; 2df ($p = 0.63$)				1.0[c]; 2df ($p = 0.60$)		
Number of induced abortions[h]							
per abortion	1.2	1.1	–	1.0	1.2	1.1	1.0
χ^2		0.9[b]; 2df ($p = 0.65$)			3.4[c]; 2df ($p = 0.70$)		
Outcome of first pregnancy[g]							
Nulligravidae	1[e]	1[e]	–	–	1[e]	1[e]	1[e]
Birth	1.2	1.8	–	–	1.4	1.3	1.2
Induced abortion	1.2	1.8	–	–	0.9	1.8	1.2
Miscarriage	1.6	2.4	–	–	2.1	1.6	1.6
χ^2		2.3[b]; 3df ($p = 0.51$)			3.8[c]; 6df ($p = 0.70$)		
History of infertility[h]							
Yes *vs* No	1.0	2.2	–	2.0	1.6	1.3	0.9
χ^2		2.5[b]; 2df ($p = 0.29$)			3.5[c]; 2df ($p = 0.17$)		
Age at first birth[h]							
per 5 year delay	1.0	1.2	1.1	1.3	1.3	1.2	1.0
χ^2		1.9[b]; 3df ($p = 0.60$)			4.0[c]; 2df ($p = 0.14$)		
Age at last birth[h]							
per 5 years increase	1.0	1.0	1.0	1.2	1.4	1.0	1.0
χ^2		4.5[b]; 3df ($p = 0.22$)			6.9[c]; 2df ($p = 0.03$)		
Years since last birth[h] (women aged ≤ 45 years only)							
per 5 years increase	0.6	1.1	0.8	0.8	0.8	0.9	–
χ^2		1.5[b]; 3df ($p = 0.68$)			0.8[c]; 1df ($p = 0.37$)		
Breast feeding[i]							
per 12 months	0.9	1.2	1.1	0.9	0.9	1.0	1.1
χ^2		5.6[b]; 3df ($p = 0.13$)			1.1[c]; 2df ($p = 0.57$)		

[a] Estimates from conditional logistic regression conditioning on study and age, adjusted for history of radiation and age.
[b] Testing heterogeneity across geographical areas.
[c] Testing effect modification of age.
[d] Adjusted also for use of hormone replacement therapy.
[e] Reference category.
[f] Adjusted also for type of menopause.
[g] Adjusted also for oral contraceptives use.
[h] Adjusted also for parity.
[i] Adjusted also for parity and use of hormones for lactation suppression.

Discussion

Several menstrual and reproductive factors have been related to thyroid cancer risk, however, many of these results are inconsistent. This is not surprising, since available data on menstrual and reproductive factors indicate that these factors are, at most, moderately related to thyroid cancer risk. Even the few significant associations observed (*i.e.*, with later menarche, miscarriage as a first pregnancy or later age at first birth) were weak.

The present pooled analyses were based on a uniquely large dataset for a relatively rare neoplasm such as thyroid cancer. For age at first birth, time since last birth, and infertility, the associations observed are in the same direction as those reported for breast cancer, but of smaller magnitude [34, 35]. In contrast, unlike breast cancer, there appears to be an inverse relationship between thyroid cancer and age at menopause. Effects of most menstrual and reproductive factors occured at younger age at diagnosis and, as in several other hormone-related neoplasms, their effect seems to level off after stopping exposure [36].

Some of the risks observed, including artificial menopause, may well be due to surveillance bias, since women undergoing surgical menopause may be more carefully monitored for any hormonal – including thyroid – imbalances, particularly during the first few years after surgery [37]. The increased risk of artificial menopause, however, could be related to an underlying clinical condition, which, as in the case of uterine fibroma, results in hyperestrogenism [25]. Other factors, including age at first birth or time since last birth, are less likely to be influenced by ascertainment or recall bias, and probably reflect real indicators of thyroid cancer risk. In fact, it is unlikely that the recall of parity-related factors is systematically different for cases and controls.

The absence of significant heterogeneity across studies or geographic areas provides further support for the observed associations. The lack of appreciable associations observed with infertility, miscarriages, nulliparity or breast feeding are also of interest, since these factors have been reported in some previous studies [37, 38].

In conclusion, the present study provides more precise results than previously available on the role of menstrual and reproductive factors on thyroid carcinogenesis. The data suggest that menstrual and reproductive factors are, if anything, weakly related with thyroid cancer risk.

Acknowledgements

The contributions of the Italian Association for Cancer Research, Milan, Italy, and of the United States National Cancer Institute are gratefully acknowledged. Ms M. Paola Bonifacino and G.A. Pfeiffer Memorial Library staff provided editorial assistance.

References

1. dos Santos Silva I, Swerdlow AJ (1993) Sex differences in the risks of hormone-dependent cancers. *Am J Epidemiol* **138**: 10–28.
2. Correa P, Chen VW (1995) Endocrine gland cancer. *Cancer* **75**: 338–352.
3. Malkasian GD, Mayberry WE (1970) Serum total and free thyroxine and thyrotropin in normal and pregnant women, neonates, and women receiving progestogens. *Am J Obstet Gynecol* **108**: 1234–1238.
4. Rastogi GK, Sawhney RC, Sinha MK, *et al.* (1974) Serum and urinary levels of thyroid hormones in normal pregnancy. *Obstet Gynecol* **44**: 176–180.
5. Chan V, Paraskevaides CA, Hale JF (1975) Assessment of thyroid function during pregnancy. *Br J Obstet Gynaecol* **82**: 137–141.
6. Pacchiarotti A, Martino E, Bartalena L, *et al.* (1986) Serum thyrotropin by ultrasensitive immunoradiometric assay and serum free thyroid hormones in pregnancy. *J Endocrinol Invest* **9**: 185–189.
7. Henderson BE, Ross RK, Pike MC, *et al.* (1982) Endogenous hormones as a major factor in human cancer. *Cancer Res* **42**: 3232–3239.
8. Williams ED (1990) TSH and thyroid cancer. *Horm Metab Res Suppl* **23**: 72–75.
9. Robbins SL, Cotram RS, Kumar V (1984) *Pathologic Basis of Disease*. *Thyroid Gland*. Philadelphia: WB Saunders, pp. 1201–1225.
10. Chaudhuri PK, Prinz R (1989) Estrogen receptor in normal and neoplastic human thyroid tissue. *Am J Otolaryngol* **10**: 322–326.
11. Miki H, Oshimo K, Inoue H, Morimoto T, Monden Y (1990) Sex hormone receptors in human thyroid tissues. *Cancer* **66**: 1759–1762.
12. Takeichi N, Ito H, Haruta R, *et al.* (1991) Relation between estrogen receptor and malignancy of thyroid cancer. *Jpn J Cancer Res* **82**: 19–22.
13. Mori M, Naito M, Watanabe H, *et al.* (1990) Effects of sex difference, gonadectomy, and estrogen on N-methyl-N-nitrosourea induced rat thyroid tumors. *Cancer Res* **50**: 7662–7667.
14. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE (1987) Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Br J Cancer* **55**: 191–195.
15. Levi F, Franceschi S, Gulie C, Negri E, La Vecchia C (1993) Female thyroid cancer: the role of reproductive and hormonal factors in Switzerland. *Oncology* **50**: 309–315.
16. Preston-Martin S, Jin F, Duda MJ, Mack WJ (1983) A case-control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). *Cancer Causes Control* **4**: 431–442.

17. Wingren G, Hatschek T, Axelson O (1993) Determinants of papillary cancer of the thyroid. *Am J Epidemiol* **138**: 482–491.
18. Glattre E, Kravdal Ø (1994) Male and female parity and risk of thyroid cancer. *Int J Cancer* **58**: 616–617.
19. McTiernan AM, Weiss NS, Daling JR (1984) Incidence of thyroid cancer in women in relation to reproductive and hormonal factors. *Am J Epidemiol* **120**: 423–435.
20. Ron E, Kleinerman RA, Boice JD Jr, *et al*. (1987) A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* **79**: 1–12.
21. Franceschi S, Fassina A, Talamini R, *et al*. (1990) The influence of reproductive and hormonal factors on thyroid cancer in women. *Rev Epidém Santé Publ* **38**: 27–34.
22. Kolonel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW (1990) An epidemiological study of thyroid cancer in Hawaii. *Cancer Causes Control* **1**: 223–234.
23. Hallquist A, Hardell L, Degerman A, Boquist L (1994) Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. A case-control study. *Eur J Cancer Prev* **3**: 481–488.
24. Kravdal O, Glattre E, Haldorsen T (1991) Positive correlation between parity and incidence of thyroid cancer: new evidence based on complete Norwegian birth cohorts. *Int J Cancer* **49**: 831–836.
25. Galanti MR, Lambe M, Ekbom A, Sparén P, Pettersson B (1995) Parity and risk of thyroid cancer: a nested case-control study of a nationwide Swedish cohort. *Cancer Causes Control* **6**: 37–44.
26. Galanti MR, Hansson L, Lund E, *et al*. (1996) Reproductive history and cigarette smoking as risk factors for thyroid cancer in women: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* **5**: 425–431.
27. Paoff K, Preston-Martin S, Mack WJ, Monroe K (1995) A case-control study of maternal risk factors for thyroid cancer in young women (California, United States). *Cancer Causes Control* **6**: 389–397.
28. Negri E, Ron E, Franceschi S, *et al*. A pooled analysis of case-control studies of thyroid cancer. I. Methods. *Cancer Causes Control* **10**: 131–142.
29. Galanti MR, Hansson L, Bergstrom R, *et al*. (1997) Diet and nutrients as risk factors for papillary and follicular thyroid carcinoma. *Cancer Causes Control* **8**: 205–214.
30. Glattre E, Haldorsen T, Berg JP, Stensvold I, Solvoll K (1993) Norwegian case-control study testing the hypothesis that seafood increases the risk of thyroid cancer. *Cancer Causes Control* **4**: 11–16.
31. Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA (1989) Does coffee consumption protect against thyroid diseases? *Acta Chir Scand* **155**: 317–320.
32. Breslow NE, Day NE (1980) *Statistical Methods in Cancer Research, Vol. 1, The Analysis of Case-Control Studies*. Lyon, IARC: IARC Sci. Publ. No. 32.
33. Collaborative Group on Hormonal Factors on Breast Cancer. (1996) Breast cancer and hormonal contraceptives. *Lancet* **347**: 1713–1727.
34. Kelsey JL, Gammon MD, John EM (1993) Reproductive factors and breast cancer. *Epidemiol Rev* **15**: 36–47.
35. Lipworth L (1995) Epidemiology of breast cancer. *Eur J Cancer Prev* **4**: 7–30.
36. Day NE (1983) Time as a determinant of risk in cancer epidemiology: the role of multi-stage models. *Cancer Surveys* **2**: 577–593.
37. Franceschi S, Boyle P, Maisonneuve P, *et al*. (1993) The epidemiology of thyroid carcinoma. *Crit Rev Oncogen* **4**: 25–52.
38. Ron E (1996) Epidemiology of thyroid cancer. In: Schottenfeld D, Fraumeni JR Jr. *Cancer Epidemiology Prevention*. Oxford: Oxford University Press, pp. 1000–1021.